1083-8791/07/1306-0001$32.00/0
doi:10.1016/j.bbmt.2007.02.001

ASBMT American Society for Blood and Marrow Transplantation

Bisphosphonate Therapy for Reduced Bone Mineral Density in Children with Chronic Graft-versus-Host Disease

Paul A. Carpenter,[1,2] *Paul Hoffmeister*,[1] *Charles H. Chesnut III*,[2] *Barry Storer*,[1,2] *Paula M. Charuhas*,[3] *Ann E. Woolfrey*,[1,2] *Jean E. Sanders*,[1,2]

[1]Fred Hutchinson CRC and [2]University of Washington, and [3]Seattle Cancer Care Alliance, Seattle, Washington

Correspondence and reprint requests: Paul A. Carpenter, MD, Fred Hutchinson CRC, Clinical Research Division, 1100 Fairview Avenue North, Mailstop D5-290, Seattle, WA 98109 (e-mail: pcarpent@fhcrc.org).

Received November 21, 2006; accepted February 5, 2007

ABSTRACT

Reduced bone mineral density (BMD) occurs frequently in children after hematopoietic cell transplantation (HCT), but therapy for this complication is undefined. To determine the impact of bisphosphonate therapy on reduced BMD after HCT, we compared baseline and follow-up dual energy X-ray absorptiometry (DEXA) scans of 48 patients (controls) who received calcium and vitamin D to 18 patients who also received bisphosphonate therapy. Among the controls, median annualized increase in standardized BMD (sBMD) was 10% (range, −26% to +41%), but the deviation of sBMD from normal, as indicated by the *Z*-score, did not improve from baseline, −2.46 (range: −5.15 to −1.16) compared to follow-up, −2.79 (range: −5.76 to +0.07). For the bisphosphonate-treated patients, the median annualized increase in sBMD was 33% (range 3% to 147%, $P = .0002$) and the median *Z*-score improved from −3.57 (range: −5.13 to −0.86) at baseline, to −1.80 (−4.89 to +0.47) at follow-up ($P = .06$). The annualized median change in BMD *Z*-scores per year was +0.12 (−2.28 to +4.24) among the controls and +1.43 (−0.29 to +3.72) for the bisphosphonate group ($P = .0002$). The greatest improvement in BMD was observed in children who received therapy with bisphosphonates.

KEY WORDS

Bisphosphonate • Children • GVHD • Hematopoietic cell transplant • Osteopenia • Osteoporosis

INTRODUCTION

The attainment of sufficient peak bone mass during adolescence and early adulthood is an important determinant of long-term bone health, which correlates with the risk for involutional osteoporotic fractures [1, 2]. Therefore, it is of concern that almost half of the children after hematopoietic cell transplantation (HCT) have reduced bone mineral density (BMD) [3]. Dual-energy X-ray absorptiometry (DEXA) is the most common method for measuring BMD in children now that age-related normative reference data are available [4, 5]. The only study to report BMD in children after HCT using DEXA scan technology showed that BMD was significantly lower than in adults [6]. A large population-based cohort study indicates that fracture rates peak in childhood at age 14 years for boys and 11 years for girls with a combined rate of 133 per 10,000 person-years [7]. This compares with an estimated fracture rate among pediatric HCT recipients at our center of 172 per 10,000 person years (J.E. Sanders, unpublished data), suggesting that reduced BMD may be clinically relevant.

Bone loss results from impaired bone mineralization through disturbances of calcium and vitamin D homeostasis, osteoblast, and osteoclast function, and deficiencies in growth or gonadal hormone secretion. Factors responsible for these disturbances include chronic illness, glucocorticoid therapy, cranial or total-body irradiation (TBI), and other cytotoxic agents given before HCT [8-14]. The leading cause of reduced BMD after HCT is prolonged glucocorticoid therapy for graft-versus-host disease (GHVD) [8, 11, 14]. Bone loss is most rapid during

the first 6 months of glucocorticoid therapy, and may occur with daily prednisone doses as low as 5 mg [15].

The National Institutes of Health Consensus recommendations for management of bone loss in adults with chronic GVHD (cGVHD) include intake of sufficient calcium and vitamin D, and therapy with sex hormones or bisphosphonates, but the evidence for bisphosphonate use in children is limited [16, 17]. Bisphosphonates are analogs of pyrophosphate that bind to hydroxyapatite crystals, and act primarily through effects on enzymatic pathways in osteoclasts to inhibit bone resorption but may also stimulate osteoblasts to promote bone formation [18]. The use of bisphosphonates in children has largely been confined to intravenous (IV) formulations like pamidronate, based upon experience in osteogenesis imperfecta, and to a lesser extent in idiopathic juvenile osteporosis or glucocorticoid-induced osteoporosis [19-25]. We report here the impact on BMD since we began adding bisphosphonate therapy to calcium and vitamin D supplementation in children with reduced BMD after HCT.

PATIENTS AND METHODS

Study Population and Design

This restrospective study included all pediatric patients who survived at least 1 year after receiving an allogeneic HCT at the Fred Hutchinson Cancer Research Center (FHCRC) between January 1997 and June 2004. Patients or their responsible guardians, consented to the Protocol 999.02 approved by the institutional review board of the FHCRC. Among the 238 children who survived >1 year, 173 had a screening DEXA scan and 55 did not. Ninety-nine (57%) of the 173 screened patients had osteopenia or osteoporosis based on the following definition: osteopenia is present when a child's BMD in g/cm^2 equates to a Z-score of -1.0 to 2.4 standard deviations below age-related mean BMD values, and osteoporosis is present when the Z-score is ≤ -2.5. Among these 99 patients, 58 had 2 or more DEXA scans during long-term follow-up and were selected for analysis. Patients were then grouped according to whether or not they received bisphosphonate therapy. Forty-eight patients who received supplemental vitamin D, and dietary calcium with supplementation as appropriate (controls), were compared to 18 patients who received additional therapy with bisphosphonate. Eight patients who failed to maintain BMD with calcium and vitamin D supplements subsequently received bisphosphonate therapy and were analyzed twice in separate treatment groups.

Medications for Prevention or Treatment of Osteopenia

As part of long-term follow-up a clinical nutritionist assessed each child's calcium and vitamin D intake based upon review of food records at almost every visit throughout the study interval. Supplemental calcium was prescribed for children receiving glucocorticoid therapy whenever daily calcium losses were increased, or when elemental calcium intake was less than the recommended daily intake of 800 milligrams, 1200 milligrams, or 1500 milligrams, respectively, for ages 1-5 years, 6-8 years, or >9 years old [26]. Oral vitamin D supplements were recommended whenever dietary vitamin D intake was less than the recommended daily intake of 400 international units (IU) per day for children aged 1-8 years or 400-800 IU per day for children aged 9-18 years. Pamidronate was administered monthly, at a dose of 1 milligram per kilogram of body weight, and was diluted in normal saline to a concentration of 0.12-0.36 mg/mL before infusion over 2 to 3 hours. For convenience, orally administered alendronate, or zoledronic acid by short i.v. infusion, were occasionally used as alternatives to pamidronate. Bisphosphonate was given until normal BMD was achieved and glucocorticoid therapy had been discontinued. The initiation and management of hormone replacement therapies were determined by a pediatric endocrinologist.

Bone Mineral Density Assessment

Bone mineral density was measured by DEXA at the lumbar spine and 1 or both proximal femurs using the Lunar DPX-Alpha (Madison, WI) or the Hologic QDR-4500 (Waltham, MA), depending on which machine was available at the time of baseline and follow-up evaluations. BMD was measured for 44 (67%) of the 66 patients on both occasions using a device by the same manufacturer (Hologic 35 patients, Lunar 9 patients). Six of 18 patients treated with bisphosphonates and 16 of 48 patients from the control group had follow-up scans done on a DEXA device from the alternative manufacturer. Absolute BMD in g/cm^2 was converted to standardized BMD (sBMD) expressed as mg/cm^2 using accepted formulae to account for the 12% reproducible variability in BMD when DEXA devices are used from different manufacturers [27, 28]. Thus, $sBMD_{SPINE} = 1000 (0.9522 \times \text{Lunar DPX-L } BMD_{SPINE})$ and $sBMD_{SPINE} = 1000 (1.0755 \times \text{Hologic QDR-2000 } BMD_{SPINE})$. Because normative reference ranges for BMD using the Hologic machine were not available across a broad range of pediatric ages, BMD analyses were confined to a comparison of average BMD measured at the 2nd, 3rd, and 4th lumbar vertebrae.

Table 1. *Patient Demographics*

Bisphosphonate Therapy	No	Yes	*P*
Number of patients	48	18	—
Male gender	29	11	.96
Age, years, median (range)			
At transplant	10.0 (1.1-17.9)	11.3 (5.9-17.1)	.04
At baseline DEXA	10.4 (2.0-18.2)	12.0 (7.9-17.6)	.006
Diagnosis at transplant			
Acute lymphoblastic leukemia	21	8	.96
Non-ALL	27	10	—
Preparative regimen			
Myeloablative TBI-containing	32	14	.62
Myeloablative chemotherapy only	10	3	—
Nonmyeloablative	6	1	—

TBI indicates total body irradiation; ALL, acute lymphoblastic leukemia; DEXA, dual energy X-ray absorptiometry.

Statistics

Descriptive statistics were tabulated for relevant patient characteristics known to influence BMD. The chi-square test was used to compare categoric and the *t*-test was used to compare continuous data. The Wilcoxon test was used for the comparison of BMD after bisphosphonate with or without growth hormone therapy. For patients who were evaluated both with and without bisphosphonate, the data associated with each treatment period were assigned separately to the appropriate treatment group. For simplicity, the comparisons between groups were conducted as if they were fully independent.

RESULTS

Baseline and Interval Characteristics

Fifty-eight patients predominantly received myeloablative conditioning and marrow transplantation for leukemia at a median age of 10.6 years (range: 1.1-17.9 years). Sixty percent of the study cohort was male and the proportion of males to females was similar for both groups (Table 1). Subjects with acute lymphoblastic leukemia (ALL) had the greatest exposure to glucocorticoids before HCT and were distributed evenly between groups. More children in the control group had received a transplant for a nonmalignant disorder. Cord blood recipients who received glucocorticoids for acute GVHD (aGVHD) prophylaxis numbered 5 among the controls, and 4 in the bisphosphonate group. cGVHD was present in 74% of subjects and with a trend towards higher incidence in those treated with bisphosphonates ($P = .10$). An apparently greater proportion of children treated with bisphosphonates had received glucorticoid therapy for more than half of the study interval ($P = .17$; Table 2). Compared to the control group, more children who received bisphosphonates were receiving growth hor-

Table 2. *Interval Study Characteristics*

Bisphosphonate Therapy	No	Yes	*P*
Chronic GVHD			
Yes, n (%)	33 (69)	16 (89)	.10
No, n (%)	15 (31)	2 (11)	—
Pertinent medications			
Growth hormone, n	4	6	.01
Thyroxine, n	2	1	.81
Sex-hormone replacement, n	3	3	.19
Prednisone <50% of interval*, n	21	3	—
Prednisone >50% of interval*, n (%)	27 (56)	15 (83)	.17
Calcium repletion			
Not required, n	10	2	—
Partial interval supplementation			
n	7	1	—
Median dose, mg (range)	358 (0-2400)	1000 (0-2400)	—
Full interval supplementation			—
n	31	15	—
Median dose, mg (range)	1000 (0-2400)	1500 (0-2400)	—
Vitamin D repletion			
Full interval supplementation, n	48	18	—

GVHD indicates graft-versus-host disease.

*Patients were stratified according to whether the duration of prednisone therapy spanned ≥50%, or <50%, of the study interval.

Table 3. *Interval Study Outcomes*

Bisphosphonate Therapy	No		Yes		
Outcome	Median	Range	Median	Range	P
Study Interval (days)	299	197-1302	377†	226-788	.46
Age at follow-up DEXA (y)	11.5	3.8-18.7	13.0	9.1-18.9	.009
Height velocity percentile	25th	<3rd->99th	<3rd	<3rd->99th	.16
Pubertal progression					
Tanner stage at baseline	1	1-5	2	1-5	.50
Tanner stage at follow-up	1.5	1-5	2	1-5	.43
Standardized BMD (mg/cm^2)					
Baseline	+585	+338-+982	+623	+364-+1016	.28
Follow-up	+624	+364-+1086	+832	+497-+1083	.001
Increase in sBMD per year	+60	−137-+261	+174	+17-+369	.0002
sBMD/y, prednisone use <50%*	+76	0-+261	+253	+160-+369	.10
sBMD/yr, prednisone use >50%*	+50	−137-+192	+169	+17-+332	.0003
BMD *Z*-score					
Baseline	−2.46	−5.15-−1.16	−3.57	−5.13-−0.86	.02
Follow-up	−2.79	−5.56-+0.07	−1.80	−4.89-+0.47	.06
Increase in *Z*-score per year	+0.12	−2.28-+4.24	+1.43	−0.29-+3.72	.0002

sBMD indicates standardized bone mineral density; BMD, bone mineral density; DEXA, dual energy X-ray absorptiometry.
*Patients were stratified according to whether the duration of prednisone therapy spanned ≥50%, or <50%, of the study interval.
†The median length of bisphosphonate therapy was 351 days (range: 188-770).

mone (P = .01). At the time of the baseline DEXA scan, puberty was similarly advanced despite the median age being older among children receiving bisphosphonates compared to controls (Table 3). The median height velocity percentile by the end of the study did not differ significantly between groups (P = .16).

All children received daily supplementation with at least 400 IU of vitamin D (range 400-1200 IU). Twelve children did not require calcium supplementation and 53 received partial or full supplementation with calcium based upon dietary intake and estimated losses (Table 2).

Seventeen of the 18 children who were treated with bisphosphonate received pamidronate for the majority of the study interval. In 2 children, pamidronate was later changed by the referring physician to i.v. zoledronic acid. Two teenage patients began therapy with oral alendronate, but 1 patient showed gastrointestinal intolerance and was changed to pamidronate. Two other teenage patients were changed to alendronate for the convenience of oral administration late in the course of therapy.

Response to Therapy

The absolute change in BMD over the study interval was examined by comparing sBMD to account for differences in BMD that might have been attributed to the 1/3 of patients whose interval comparisons were based upon data from 2 different DEXA devices (Figure 1A). The median increase in sBMD was greater in the bisphosphonate treated patients than in the controls (P = .001, Table 3). To account for the longer study interval in the bisphosphonate-treated patients the change in sBMD was annualized and was +33% per year (range: +3% to +147%) for the bisphosphonate group compared to +10% per year (range: −26% to +41%) for the controls (P = .0002; Figure 1B). The annual increase in BMD was most significant among the recipients of bisphosphonates in whom the duration of prednisone therapy was more than half of the study interval (P = .0003). However, there was a trend for bisphosphonate therapy to improve sBMD among patients who received shorter treatment with prednisone (P = .10). Because of the imbalance in the proportion of patients who were receiving growth hormone (GH) in each group we evaluated the effect of GH on sBMD. The median annualized improvement in sBMD was 45% (range: 14% to 147%) for the 6 patients treated with bisphosphonate plus GH (data not shown), and 31% (range: 3% to 59%) for the 12 patients who received only bisphosphonate (P = .15).

To account for expected age-related improvement in BMD we also examined the interval change in BMD by comparing BMD standard deviation *Z*-scores. The median interval change in the *Z*-score was +0.12 for the controls and +1.55 for patients who received bisphosphonates (Figure 2A). The annualized median change in the *Z*-score was +0.12 per year for the control group and +1.43 per year for the bisphosphonate group (P = .0002; Figure 2B). Within the control group, the annualized median change in *Z*-score was no different between children who did or did not require supplemental calcium and vitamin D (data not shown).

Six children (12.5%) from the control group developed bone fractures at a median of 2.3 years (range: 0.9-5.5 years) from baseline. Fractures were noted in vertebral bodies, clavicle, and extremities, excluding the phalanges. Two children (11%) from the group

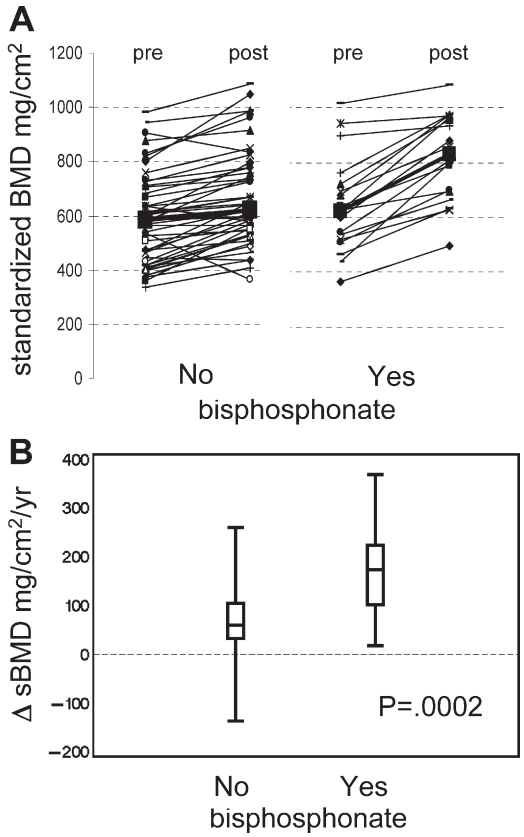

Figure 1. Bone mineral density at baseline and after follow-up. Shown for the patients treated without (n = 48) and with (n = 18) bisphosphonates are: (A) the standardized BMD (sBMD) for each patient, together with the median sBMD (filled large squares), at baseline (pre) and at follow-up (post), and (B) the median, 25th, and 75th percentiles (box), and range of the rates of change of sBMD (whiskers).

treated with bisphosphonates developed fractures. One child with severe osteoporosis at baseline (*Z*-score, −5.13) had marked improvement in BMD but fractured their right patella and radius during treatment with bisphosphonate when they still had moderately severe osteopenia (*Z*-score, −1.88). The other child whose *Z*-score improved from −3.37 to +0.47 developed an avulsion fracture of the fifth metatarsal 4 months after stopping bisphosphonate therapy.

Drug-Related Toxicities

Monthly infusions of pamidronate were well tolerated with no related episodes of fever, hypocalcemia, hypophosphatemia, or deterioration in serum creatinine. Grade 1 (CTC v 3.0) hypomagnesemia was present in many patients because of concomitant calcineurin inhibitor therapy, but there was no discernable acute or chronic disturbance of magnesium homeostasis related to bisphosphonate infusions. One patient developed a pruritic skin reaction with the first infusion of pamidronate. Another patient developed dyspepsia with oral alendronate. No patients developed osteonecrosis of the jaw (ONJ). The development of transverse bands of osteosclerosis as an incidental finding on plain film radiographs of long bones was common among the children who received bisphosphonates.

DISCUSSION

To the best of our knowledge, these results are the first to compare intervention with bisphosphonate versus standard calcium and vitamin D replacement as therapy for children with reduced bone mineral density after HCT. In growing children, area-related BMD at the lumbar spine increases annually by 2%-7% before puberty and 9%-13% during puberty based upon available normative data [29, 30]. We found that bisphosphonate therapy resulted in a 33% median annualized improvement in BMD; 3-fold higher than in children receiving calcium and vitamin

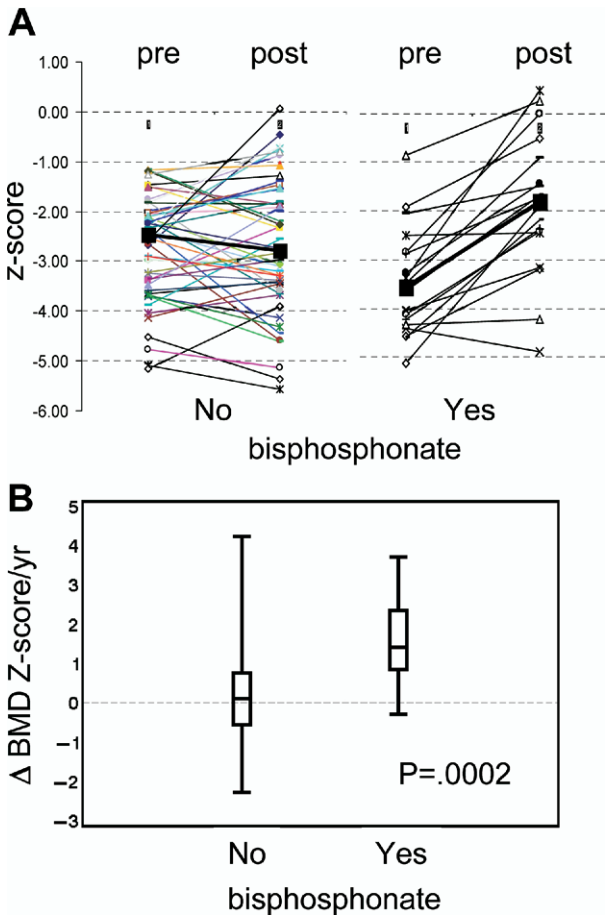

Figure 2. Annualized bone mineral density at baseline and after follow-up. Shown for the patients treated without (n = 48) and with (n = 18) bisphosphonates are: (A) the BMD *Z*-scores for each patient, together with the median *Z*-score (filled large squares), at baseline (pre) and at follow-up (post), and (B) the median, 25th, and 75th percentiles (box), and range of the rates of change of *Z*-scores (whiskers).

D alone. In children, increases in bone volume resulting from normal growth are detected by DEXA as increased areal-BMD, which may overestimate any true increase in bone mineralization because of therapy. However, our observation that BMD *Z*-scores improved in all but 1 patient who received bisphosphonates suggests that age-related changes in bone volume did not explain the positive effect that bisphosphonates had on areal-BMD. This degree of improvement allowed 6 children (33%) to shift from the categories of osteoporosis (5) or osteopenia (1) to normal BMD, and more than half of the remaining children shifted from the categories of osteoporosis (10) or osteopenia (1), to osteopenia (7), less severe osteoporosis (3), or unchanged (1).

The largest experience with pamidronate in children is in osteogenesis imperfecta, a disease where the high rate of fractures causes pain and reduced ambulation. In children with osteogenesis imperfecta, average annual gains in BMD of at least 20%-40% are achievable when cycles of bisphosphonate are administered i.v. at a dose of 1-3 mg per kilogram every 1-3 months, and have been associated with a reduction in fracture rates by more than 60% [18-20, 25, 31-33]. At our center, the cumulative incidence of bone fractures at 5 years among 1180 children who survived at least 1 year after HCT was 8% (J. E. Sanders, unpublished data). A controlled study to address whether bisphosphonates might reduce fracture rates in children after HCT is not feasible because approximately 400 patients per group would be required to have 80% power to detect a difference between a fracture rate of 5% and 10%. We presume that gains in BMD *Z*-scores of more than 1 standard deviation are clinically relevant, and should reduce the risk for fractures based upon results in other relevant diseases.

It has been cautioned that prolonged administration of bisphosphonates may render bones more brittle or impair bone healing in children [34]. Partially counterbalancing this concern are studies in osteogenesis imperfecta, which have shown that bisphosphonates do not generally impair bone healing after fractures and that intrinsic material properties of the bone are not adversely affected, although delayed bone healing is more frequent after osteotomies [35, 36]. The characteristic transverse bands of osteosclerosis that we and others have observed on plain film radiographs appear to be of no clinical consequence and disappear over time [37].

Bisphosphonate therapy was well tolerated in our patients as has been the observation in other pediatric diseases associated with reduced BMD. Many studies have reported a high incidence of fever with the initial infusion of pamidronate [19, 25]. We did not observe this association, possibly because 89% of the children were also receiving therapy with prednisone when the initial doses of pamidronate were administered.

Osteonecrosis of the jaw is a well-recognized and potentially serious but rare complication of amino bisphosphonate therapy in adults (reviewed in [38]), but there have been no reports of ONJ in children who received pamidronate for osteogenesis imperfecta [39]. However, the incidence of ONJ may approach 1% when bisphosphonates are administered i.v. and monthly to adults for the management of bone malignancy, and may occur more frequently in this setting after recent dentoalveolar trauma [38, 40]. Because oral bisphosphonates have less frequently been implicated as a cause of ONJ among patients without malignant bone disease, alendronate might be preferred over pamidronate in addition to the more convenient route of administration. Recent data indicate that oral alendronate is tolerable and improves BMD when given weekly to children who are not concomitantly receiving glucocorticoid therapy [24, 41]. However, the need to sit or stand upright for 30 minutes after swallowing alendronate to prevent esophagitis, and the risk for aspiration are practical limitations in small children. Despite the greater association of ONJ with i.v. bisphosphonates, we favor medically supervised i.v. pamidronate over weekly oral bisphosphonate to maximize compliance.

Our study had limitations associated with a retrospective analysis. Not all patients with reduced BMD were included in the analysis because they lacked a follow-up DEXA scan. Follow-up data in these patients may have altered our overall outcomes. Ideally, comparison data would have been obtained on identical DEXA machines for all patients. However, this problem was reasonably addressed by applying recognized formulae to correct for machine differences. Certain pretreatment characteristics that might have affected outcomes were not balanced through randomization into study groups. However, the only significant imbalance was the proportion of patients receiving GH therapy and a trend towards more sex hormone replacement in the bisphosphonate group. To increase sample size we pooled patients who initially received bisphosphonate therapy and those who were treated with bisphosphonates after not responding to calcium and vitamin D alone. However, there was no obvious difference between the median changes in annualized BMD *Z*-scores for the 8 patients who received bisphosphonate as secondary therapy compared to the 10 patients who received bisphosphonate as initial therapy (data not shown).

Growth hormone therapy may have contributed to the overall improvement in BMD in the bisphosphonate group because GH increases osteoblast activity and GH replacement therapy reverses osteopenia in patients with hypopituitarism [42, 43]. Mauseth et al [44] reported that BMD *Z*-scores of 23 children

who had GH deficiency and osteopenia after HCT improved significantly following treatment with GH, and adults with GH deficiency who were treated with GH had a reduced incidence of fractures [43]. Our sample size was likely insufficient to determine whether the apparent greater improvement in BMD for the 6 patients who received bisphosphonate plus GH compared to the 12 children who were treated only with bisphosphonates was real. However, the 31% median annualized improvement in sBMD for subjects who received only bisphosphonate was still 3-fold higher than the controls, suggesting that bisphosphonate therapy is efficacious by itself.

Our standard practice is to evaluate BMD in children at 3 months after allogeneic HCT with an initial follow-up DEXA scan at 1 year. It is reasonable to check the serum calcium, magnesium, and 1,25-hydroxyvitamin D level in those patients who are shown to have osteoporosis. Supplementation with calcium, vitamin D, and weight-bearing exercise based on guidelines of national organizations are recommended, although alone, these measures have not proved effective in preventing osteopenia, osteoporosis, or fractures [26, 45]. Sex hormone replacement therapy has increased bone mass in both women and men, and is recommended for adolescents if age appropriate [46, 47]. Our data provide reasonable evidence that bisphosphonate therapy is tolerable and improves BMD in children and adolescents after HCT. A large prospective study is needed to determine the incidence of osteopenia and osteoporosis in this population after HCT using DEXA, and to determine the optimal dose regimen for pamidronate.

ACKNOWLEDGMENTS

This work was supported by the NIH (grants CA18029, CA18221, and CA36444).

REFERENCES

1. Hui SL, Slemenda CW, Johnston CC Jr. The contribution of bone loss to postmenopausal osteoporosis. *Osteoporosis Int*. 1990;1:30-34.
2. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ*. 1996;312:1254-1259.
3. Kaste SC, Shidler TJ, Tong X, et al. Bone mineral density and osteonecrosis in survivors of childhood allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 2004;33:435-441.
4. Chan GM. Performance of dual-energy x ray absorptiometry in evaluating bone, lean body mass, and fat in pediatric subjects. *J Bone Miner Res*. 1992;7:369-374.
5. Gafni RI, Baron J. Overdiagnosis of osteoporosis in children due to misinterpretation of dual-energy x-ray absorptiometry (DEXA). *J Pediatrics*. 2004;144:253-257.
6. Bhatia S, Ramsay NK, Weisdorf D, et al. Bone mineral density in patients undergoing bone marrow transplantation for myeloid malignancies. *Bone Marrow Transplant*. 1998;22:87-90.
7. Cooper C, Dennison EM, Leufkens HGM, et al. Epidemiology of childhood fractures in Britain: a study using the general practice research database. *J Bone Miner Res*. 2004;19:1976-1981.
8. Stern JM, Sullivan KM, Ott SM, et al. Bone density loss after allogeneic hematopoietic cell transplantation: a prospective study. *Biol Blood Marrow Transplant*. 2001;7:257-264.
9. Weilbaecher KN. Mechanisms of osteoporosis after hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2000; 6:165-174.
10. Laan RF, van Reil PL, van de Putte LB, et al. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. *Ann Intern Med*. 1993;119:963-968.
11. Ebeling PR, Thomas DM, Erbas B, et al. Mechanisms of bone loss following allogeneic and autologous hematopoietic stem cell transplantation. *J Bone Miner Res*. 1999;14:342-350.
12. Gilsanz V, Carlson ME, Roe TF, Ortega JA. Osteoporosis after cranial irradiation for acute lymphoblastic leukemia. *J Pediatr*. 1990;117:238-244.
13. Aisenberg J, Hsieh K, Kalaitzoglou G, et al. Bone mineral density in young adult survivors of childhood cancer. *J Pediatr Hematol Oncol*. 1998;20:241-245.
14. Schulte CMS, Beelen DW. Bone loss following hematopoietic stem cell transplantation: a long-term follow-up. *Blood*. 2004; 103:3635-3643.
15. Lane NE. Osteoporosis. An update on glucocorticoid-induced osteoporosis. *Rheum Dis Clin North Am*. 2001;27:235-253.
16. Schimmer AD, Minden MD, Keating A. Osteoporosis after blood and marrow transplantation. *Biol Blood Marrow Transplant*. 2006;6:175-181.
17. Couriel D, Carpenter PA, Cutler C, et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: National institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chonic graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. *Biol Blood Marrow Transplant*. 2006;12:375-396.
18. Lindsay R. Modeling the benefits of pamidronate in children with osteogenesis imperfecta. *J Clin Invest*. 2002;110:1239-1241.
19. Glorieux FH, Bishop NJ, Plotkin H, et al. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *N Engl J Med*. 1998;339:947-952.
20. Gatti D, Antoniazzi F, Prizzi R, et al. Intravenous neridronate in children with osteogenesis imperfecta: a randomized controlled study. *J Bone Min Res*. 2005;20:758-763.
21. Gandrud LM, Cheung JC, Daniels MW, Bachrach LK. Low-dose intravenous pamidronate reduces fractures in childhood osteoporosis. *J Pediatr Endocrinol Metab*. 2003;16:887-892.
22. Unal E, Abaci A, Bober E, Buyukgebiz A. Efficacy and safety of oral alendronate treatment in children and adolescents with osteoporosis. *J Pediatr Endocrinol Metab*. 2003;19:523-528.
23. Steelman J, Zeitler P. Treatment of symptomatic pediatric osteoporosis with cyclic single-day intravenous pamidronate infusions. *J Pediatr*. 2003;142:417-423.
24. Bianchi ML, Cimaz R, Bardare M, et al. Efficacy and safety of alendronate for the treatment of osteoporosis in diffuse connective tissue diseases in children: a prospective multicenter study. *Arthritis Rheum*. 2000;43:1960-1966.
25. Thornton J, Ashcroft DM, Mughal MZ, Elliot RA, O'Neill

TW, Symmons D. Systematic review of effectiveness of bisphosphonates in treatment of low bone mineral density and fragility fractures in juvenile idiopathic arthritis. *Arch Dis Child*. 2006;91:753-761.
26. Anonymous. Recommendations for the prevention and treatment of glucocorticoid induced osteoporosis: 2001 update. American College of Rheumatologists Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. *Arthrits Rheum*. 2001;44: 1496-1503.
27. Bonnick SL. Bone density data: from DPA to DXA and manufacturer to manufacturer. In: Bonnick SL, ed. *Bone Densitometry in Clinical Practice*, 2nd ed., vol. 5. Clifton, NJ: Humana Press, 2004:111-126.
28. Pocock NA, Sambrook PN, Nguyen T, Kelly P, Freund J, Eisman JA. Assessment of spinal and femoral bone density by dual x-ray absorptiometry: comparison of Lunar and Hologic instruments. *J Bone Miner Res*. 1992;7:1081-1084.
29. Brown JJ, Zacharin MJ. Proposals for prevention and management of steroid-induced osteoporosis in children and adolescents. *J Paediatr Child Health*. 2005;41:553-557.
30. Wacker W, Barden HS. Pediatric reference data for male and female total body and spine BMD and BMC. Lunar data. International Society of Clinical Densitometry, March 13-17, 2001, Dallas, TX.
31. Plotkin H, Rauch F, Bisohp NJ, et al. Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. *J Clin Endocrinol Metab*. 2000;85:1846-1850.
32. Lee Y-S, Low S-L, Lim L-A, Loke K-Y. Cyclic pamidronate infusion improves bone mineralization and reduces fracture incidence in osteogenesis imperfecta. *Eur J Pediatr*. 2001;160: 641-644.
33. Astrom E, Soderhall S. Beneficial effect of long term intravenous bisphosphonate treatment of osteogenesis imperfecta. *Arch Dis Child*. 2002;86:356-364.
34. Marini JC. Do bisphosphonates make children's bones better or brittle? *N Engl J Med*. 2003;349:423-426.
35. Munns CF, Raunch F, Zeitlin L, Fassier F, Glorieux FH. Delayed osteotomy but not fracture healing in pediatric osteogenesis imperfecta patients receiving pamidronate. *J Bone Miner Res*. 2004;19:1779-1786.
36. Weber M, Roschger P, Fratzl-Zleman N, et al. Pamidronate does not adversely affect intrinsic material properties in children with osteogenesis imperfecta. *Bone*. 2006;39:616-622.
37. Land C, Rauch F, Glorieux FH. Cyclical intravenous pamidronate treatment affects metaphyseal modeling in growing patients with osteogenesis imperfecta. *J Bone Miner Res*. 2006;21: 374-379.
38. Sambrook P. Bisphosphonates and osteonecrosis of the jaw. *Aust Fam Physician*. 2006;35:801-803.
39. Medical Advisory Council. Bisphosphonates and the risk of osteonecrosis of the jaw in osteogenesis imperfecta. www.oif.org; August 3, 2006.
40. Woo S-B, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med*. 2006;144:753-761.
41. Ward LM, Denker AE, Porras A, et al. Single-dose pharmacokinetics and tolerability of alendronate 35- and 70-milligram tablets in children and adolescents with osteogenesis imperfecta type 1. *J Clin Endocrinol Metab*. 2005;90:4051-4056.
42. Ohlsson C, Bengtsson BA, Isaksson OG, Andreassen TT, Slootweg MC. Growth hormone and bone. *Endocr Rev*. 1998; 19:55-79.
43. Wuster C, Abs R, Bengtsson BA, et al. The influence of growth hormone deficiency, growth hormone replacement therapy, and other aspects of hypopituitarism on fracture rate and bone mineral density. *J Bone Miner Res*. 2001;16:398-405.
44. Mauseth RS, Kelly BE, Sanders JE. Bone mineral density in pediatric marrow transplant patients. *Pediatr Res*. 2001;49;82A.
45. Stallings VA. Calcium and bone health in children: a review (review). *Am J Ther*. 1997;4:259-273.
46. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA*. 2002;288:321-333.
47. Khosla S. Melton LJ, Riggs BL. Estrogens and bone health in men (review). *Calcif Tissue Int*. 2001;69:189-192.